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I, LEANNE MYNOTT, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ2661 for a patent by NOVOGEN RESEARCH PTY LTD filed on 06 September 1999.

WITNESS my hand this
Fourth day of October 2000

LEANNE MYNOTT
TEAM LEADER EXAMINATION
SUPPORT AND SALES

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Applicant(s):

Novogen Research Pty Ltd
140 Wicks Road
North Ryde New South Wales 2113
AUSTRALIA

Address for Service:

DAVIES COLLISON CAVE
Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

Invention Title:

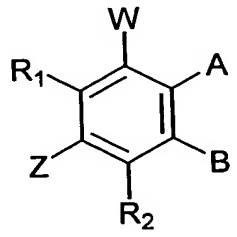
Compositions and therapeutic methods involving isoflavones and analogues thereof.

The invention is described in the following statement:

COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF

This invention relates to compounds, formulations, drinks, foodstuffs, methods and therapeutic uses involving, containing, comprising, including and/or for preparing certain isoflavone compounds and analogues thereof.

According to an aspect of this invention there is provided isoflavone compounds and analogues thereof of the by general formula I:



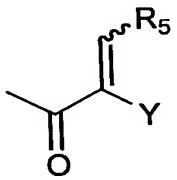
(I)

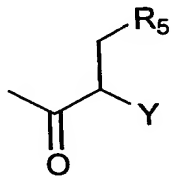
in which

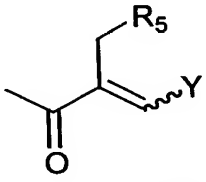
R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, $COOR_{10}$, NR_3R_4, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z is hydrogen, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

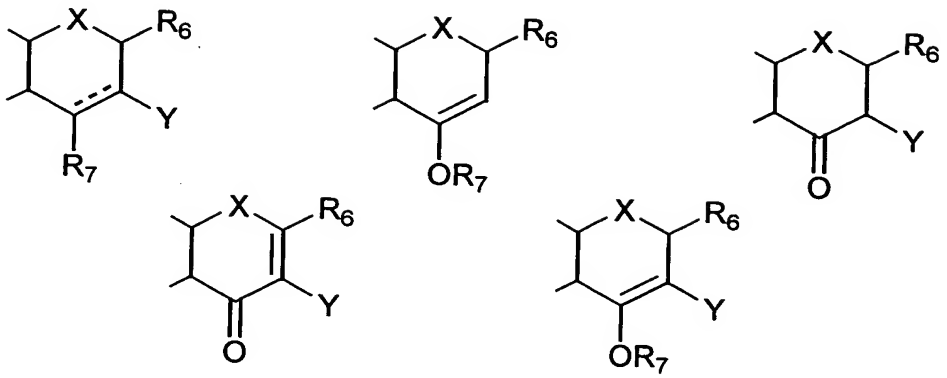






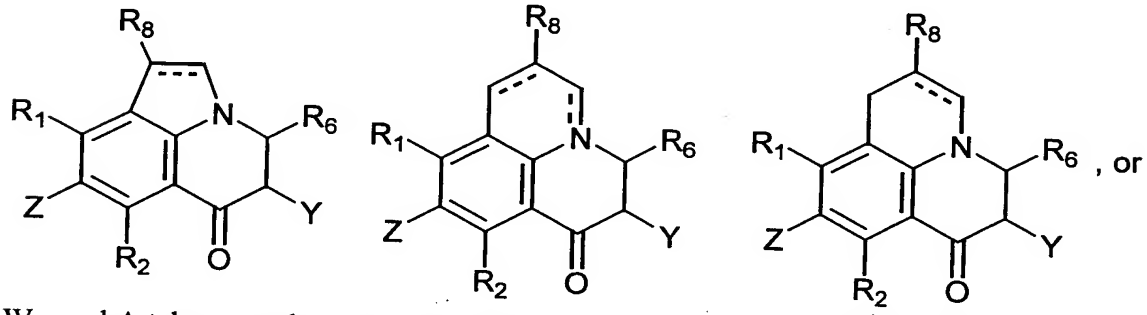
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from



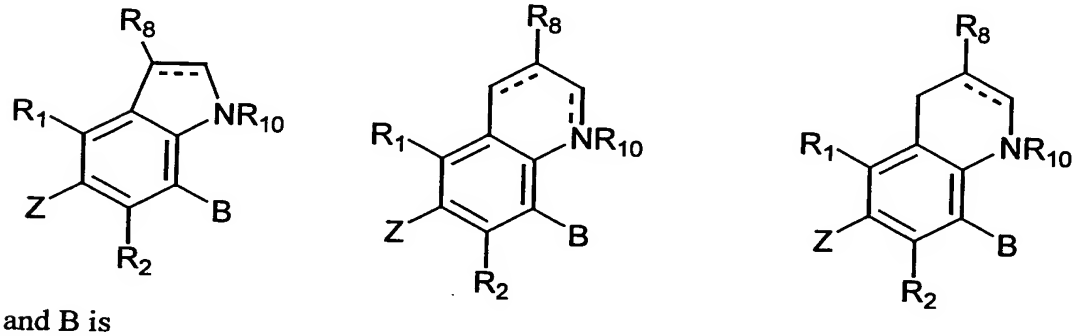
, or

W, A and B taken together with the groups to which they are associated comprise

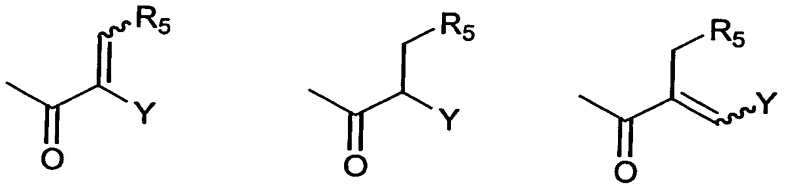


, or

W and A taken together with the groups to which they are associated comprise



and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

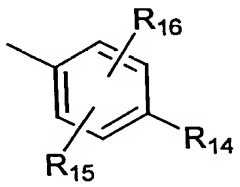
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

R_1 is hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

R_1 is hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, then

W is not hydrogen;

when

R_1 is hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

when

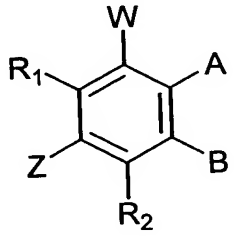
R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_1 is not hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid.

It has surprisingly been found by the inventors that compounds of the general formula I:



(I)

in which

R_1, R_2, W, A, B and Z are as defined above have particular utility and effectiveness in the treatment, prophylaxis, amelioration defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; atherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts.

Thus according to another aspect of the present invention there is provided a method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; artherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid

arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "first therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds of the formula I as defined above.

Yet another aspect of the present invention is the use of compounds of the formula I for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

Still another aspect of the present invention is the use of one or more compounds of the formula I in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

And another aspect of the present invention comprises an agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications which comprises one or more compounds of the formula I either alone or in association with one or more carriers or excipients.

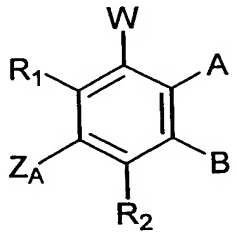
A further aspect of the invention is a therapeutic composition which comprises one or more compounds of the formula I in association with one or more pharmaceutical carriers and/or excipients.

A still further aspect of the present invention is a drink or food-stuff, which contains one or more compounds of the formula I.

Another aspect of the present invention is a microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds of the formula I.

Still another aspect of the present invention relates to one or more microorganisms which produce one or more compounds of the formula I. Preferably the microorganism is a purified culture, which may be admixed and/or administered with one or more other cultures which product compounds of the formula I.

It has also been found by the inventors that compounds of the general formula II:



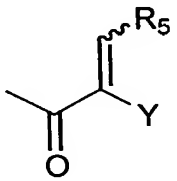
(II)

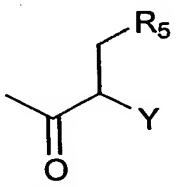
in which

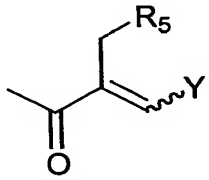
R_1 and R_2 are independently hydrogen, hydroxy, OR_{10}, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z_A is hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

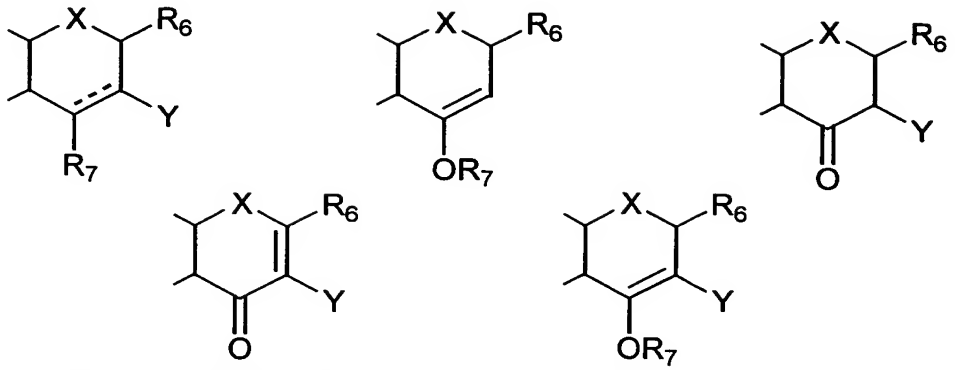






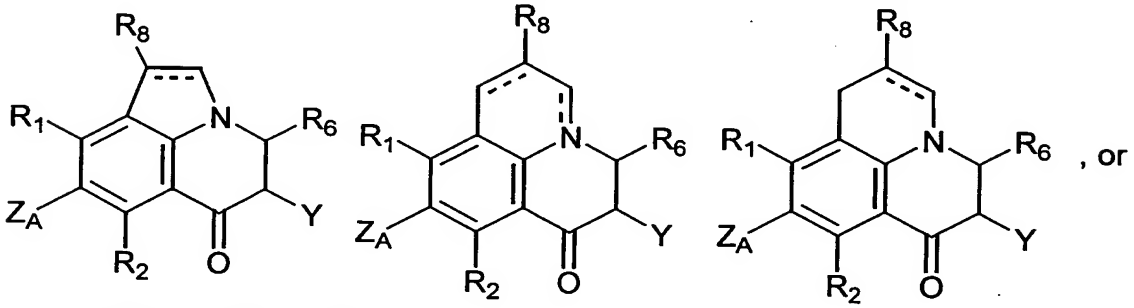
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from



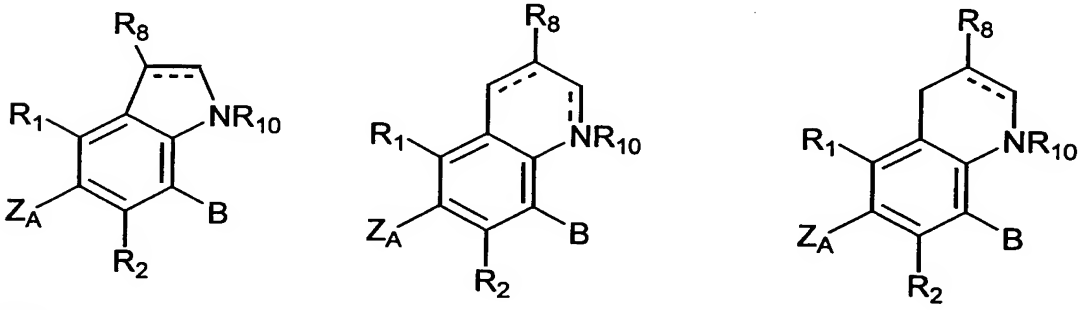
, or

W, A and B taken together with the groups to which they are associated comprise

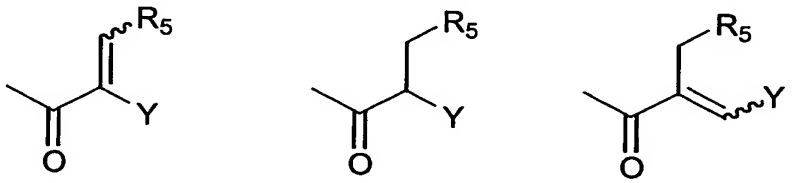


, or

W and A taken together with the groups to which they are associated comprise



and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen which they are attached are pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

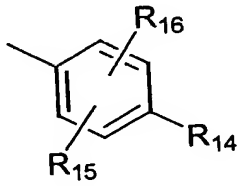
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

have particular utility and effectiveness in the treatment, prophylaxis, amelioration defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis;

premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; atherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts.

According to a another aspect of the present invention there is provided a method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; atherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "second therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds of the formula II as defined above.

Yet another aspect of the present invention is the use of compounds of the formula II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

Still another aspect of the present invention is the use of one or more compounds of the formula II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

And another aspect of the present invention comprises an agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications which comprises one or more compounds of the formula II either alone or in association with one or more carriers or excipients.

Throughout this specification and the claims which follow, unless the text requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The term "alkyl" is taken to mean both straight chain and branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, and the like. The alkyl group has 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably methyl, ethyl propyl or isopropyl. The alkyl group may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylamino-carbonyl, di-(C_1-C_4-alkyl)-amino-carbonyl, hydroxyl, C_1-C_4-alkoxy, formyloxy, C_1-C_4-alkyl-carbonyloxy, C_1-C_4-alkylthio, C_3-C_6-cycloalkyl or phenyl.

The term "aryl" is taken to include phenyl and naphthyl and may be optionally substituted by one or more C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, carbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylcarbonyloxy or halo.

The term "halo" is taken to include fluoro, chloro, bromo and iodo, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" will include monohalogenated, dihalogenated and up to perhalogenated alkyl groups. Preferred haloalkyl groups are trifluoromethyl and pentafluoroethyl.

Compounds of the present invention have particular application in the treatment of diseases associated with or resulting from estrogenic effects, androgenic effects, vasolidatory and spasmodic effects, inflammatory effects and oxidative effects.

The amount of one or more compound of formulae I and II which is required in a therapeutic treatment according to the invention will depend upon a number of factors, which include the specific application, the nature of the particular compound used, the condition being treated, the mode of administration and the condition of the patient. Compounds of formulae I or II may be administered in a manner and amount as is conventionally practised. See, for example, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1299 (7th Edition, 1985). The specific dosage utilised will depend upon the condition being treated, the state of the subject, the route of administration and other well known factors as indicated above. In general, a daily dose per patient may be in the range of 0.1 mg to 2 g; typically from 0.5 mg to 1 g; preferably from 50 mg to 200 mg.

The production of a pharmaceutical composition for the treatment of the therapeutic indications herein described (for convenience hereafter referred to as the "active compounds") are typically admixed with one or more pharmaceutically or veterinarially acceptable carriers and/or excipients as are well known in the art.

The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the subject. The carrier or excipient may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose, for example, a tablet, which may contain from 0.5% to 59% by weight of the active compound, or up to 100% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, optical, buccal (for example, sublingual), parenteral (for example, subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulation suitable for oral administration may be presented in discrete units, such as capsules, sachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture such as to form a unit dosage. For example, a tablet may be prepared by compressing or moulding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound of the free-flowing, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sublingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Compositions of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compounds, which preparations are

preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0.1% to 60% w/v of active compound and are administered at a rate of 0.1 ml/minute/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations or compositions suitable for topical administration to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combination of two or more thereof. The active compound is generally present at a concentration of from 0.1% to 0.5% w/w, for example, from 0.5% to 2% w/w. Examples of such compositions include cosmetic skin creams.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 M to 0.2 M concentration with respect to the said active compound.

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, *Pharmaceutical Research 3* (6), 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable

formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 M to 0.2 M active ingredient.

The active compounds may be provided in the form of food stuffs, such as being added to, admixed into, coated, combined or otherwise added to a food stuff. The term food stuff is used in its widest possible sense and includes liquid formulations such as drinks including dairy products and other foods, such as health bars, desserts, etc. Food formulations containing compounds of the invention can be readily prepared according to standard practices.

Compounds of the present invention have potent antioxidant activity and thus find wide application in pharmaceutical and veterinary uses, in cosmetics such as skin creams to prevent skin ageing, in sun screens, in foods, health drinks, shampoos, and the like.

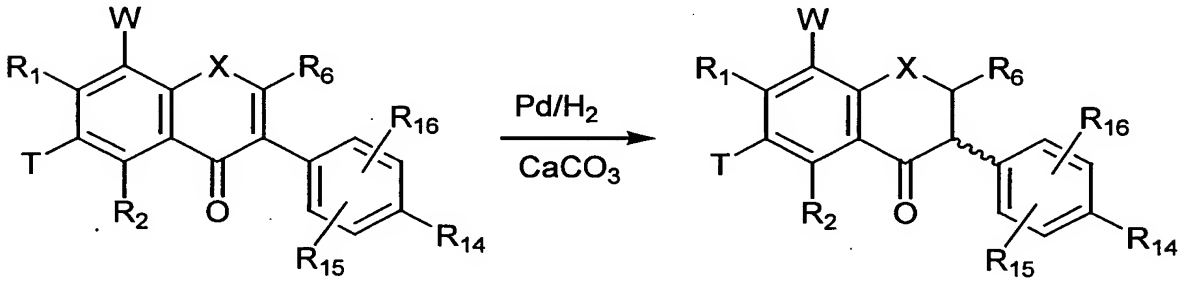
It has surprisingly been found that compounds of the formulae I or II interact synergistically with vitamin E to protect lipids, proteins and other biological molecules from oxidation.

Accordingly a further aspect of this invention provides a composition comprising one or more compounds of formulae I or II, vitamin E, and optionally a pharmaceutically, veterinarially or cosmetically acceptable carriers and/or excipients.

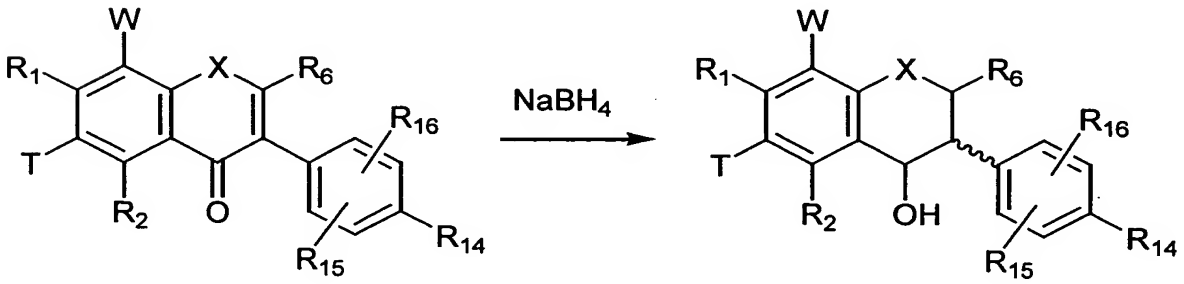
Therapeutic methods, uses and compositions may be for administration to humans or animals, such as companion and domestic animals (such as dogs and cats), birds (such as chickens, turkeys, ducks), livestock animals (such as cattle, sheep, pigs and goats) and the like.

Compounds of formulae I and II may be prepared by standard methods known to those skilled in the art. Suitable methods may be found in, for example, International Patent Application WO 98/08503 which is incorporated herein in its entirety by reference.

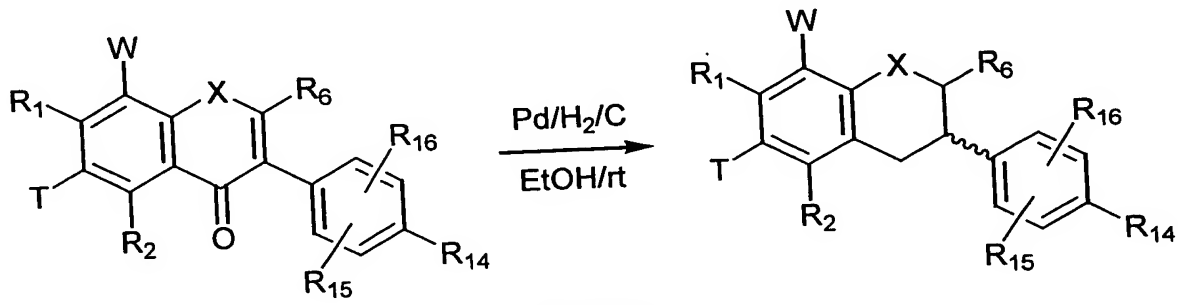
Methods which may be employed by those skilled in the art of chemical synthesis for constructing the general ring structures depicted in formulae I and II are depicted in schemes 1-8 below. Chemical functional group protection, deprotection, synthons and other techniques known to those skilled in the art may be used where appropriate in the synthesis of the compounds of the present invention. In the formulae depicted in the schemes below the moities R_1, R_2, R_6, R_8, R_{14}, R_{15}, R_{16}, W and X are as defined above. The moiety T is either Z or Z_A as defined in formulae I or II above.



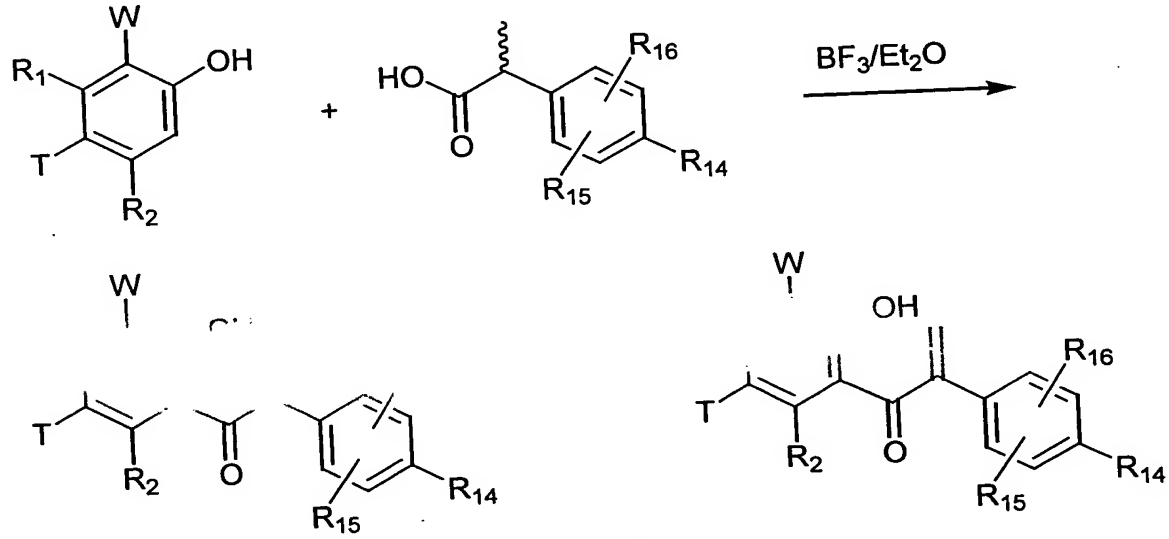
Scheme 1



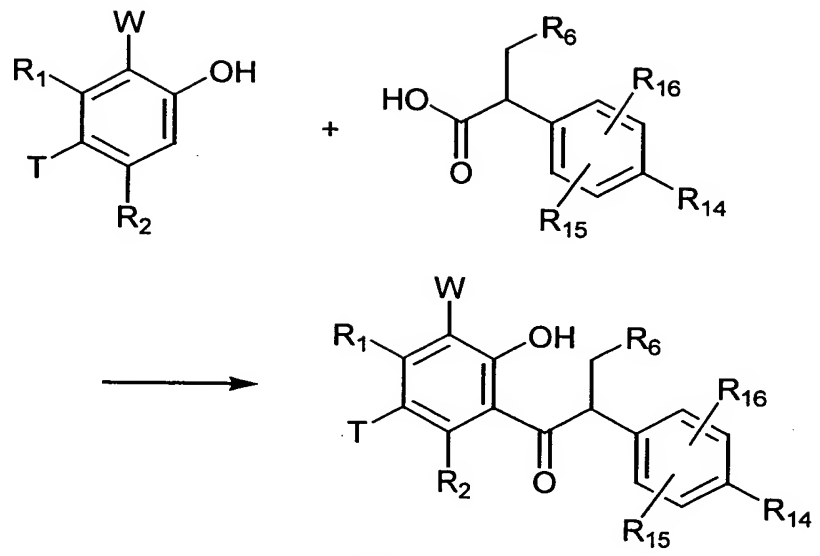
Scheme 2



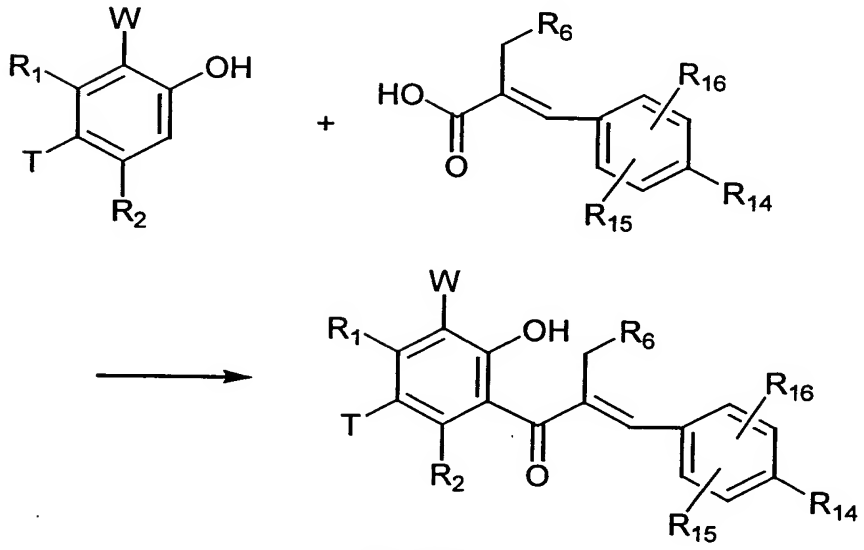
Scheme 3



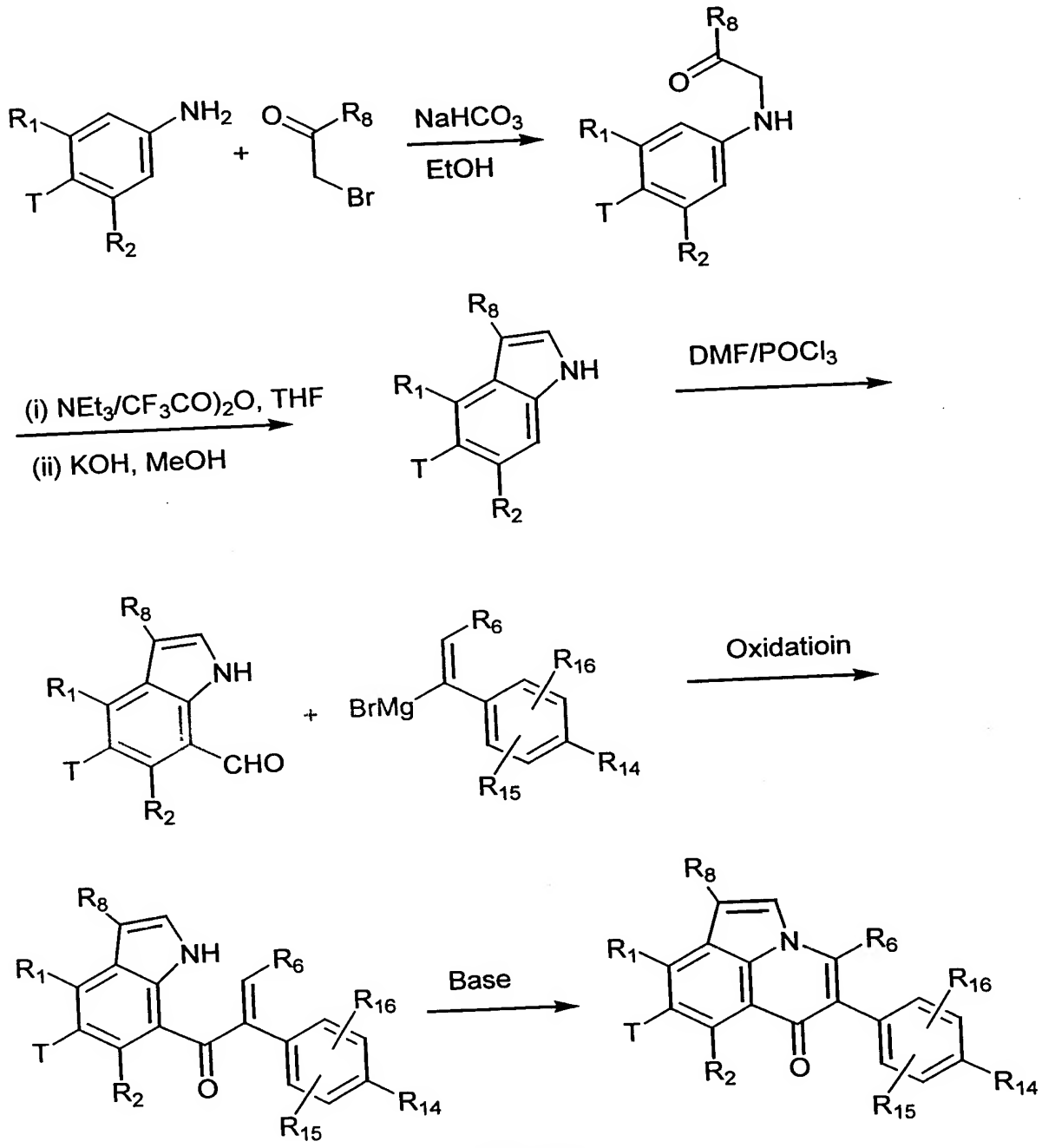
Scheme 4



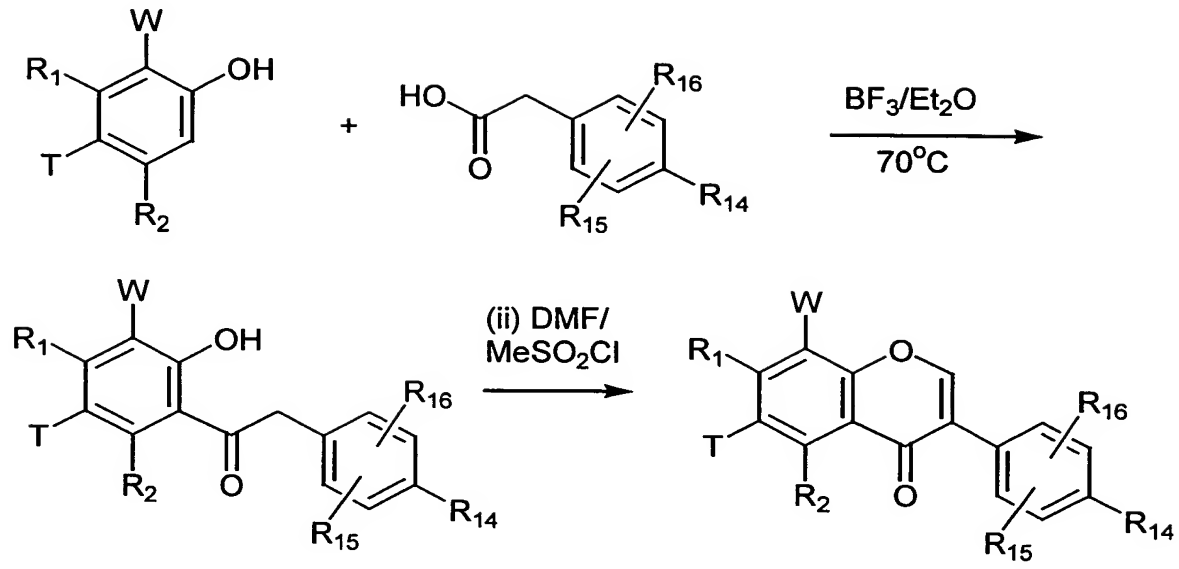
Scheme 5



Scheme 6


R1
NH2
T
R2
O
R8
Br
+
NaHCO3
EtOH
R8
O
NH
R1
T
R2
(i) NEt3/CF3CO)2O, THF
(ii) KOH, MeOH
R8
NH
R1
T
R2
DMF/POCl3
R8
NH
R1
T
CHO
R2
+
R6
BrMg
R16
R14
R15
Oxidatioin
R8
NH
R1
T
R2
R6
O
R16
R14
R15
Base
R8
N
R6
R1
T
R2
O
R16
R14
R15

Scheme 7

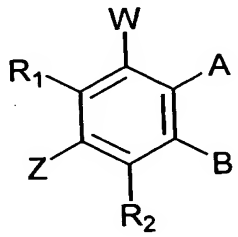


Scheme 8

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The inventions also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The claims defining the invention are as follows:

1. Isoflavone compounds and analogues thereof of the general formula I:



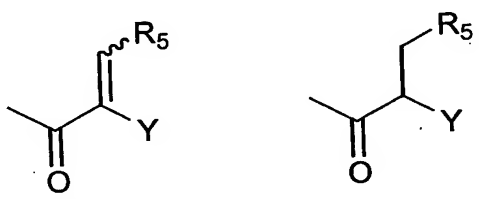
(I)

in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

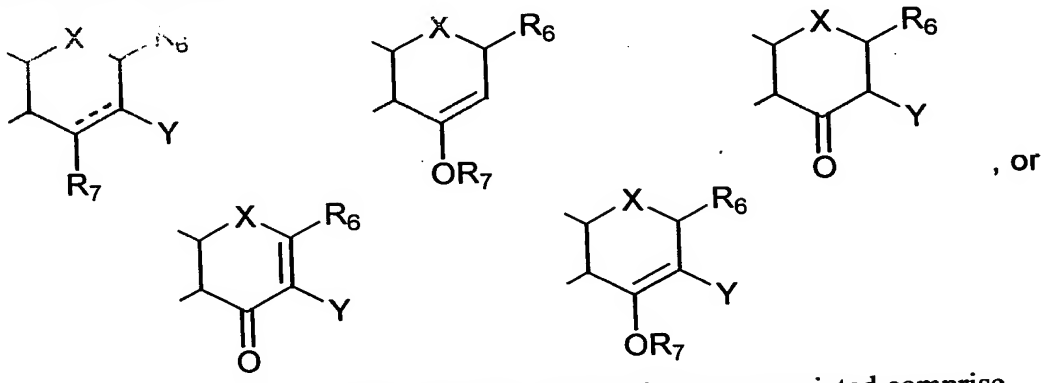
Z is hydrogen, and

W is R_1, A is hydroxy, NR_3R_4 or thio, and B is selected from



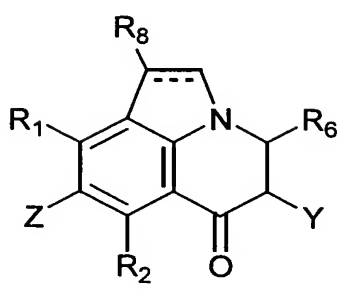
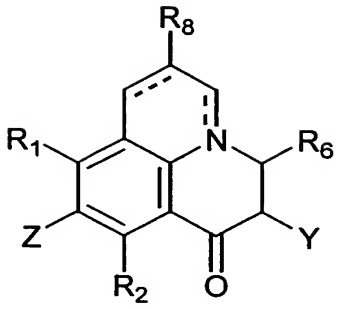
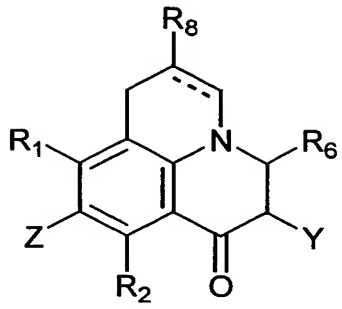
, or

W is R_1, and A and B taken together with the [illegible] which they are attached form a six-membered [illegible]

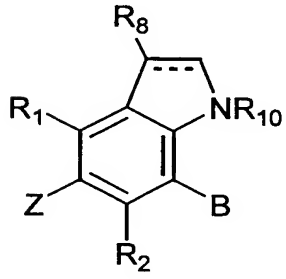
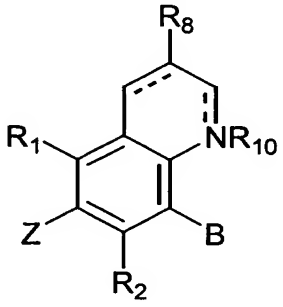
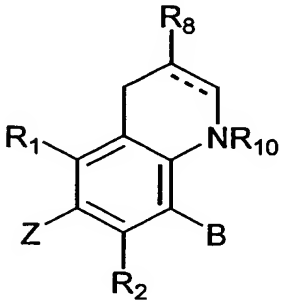


, or

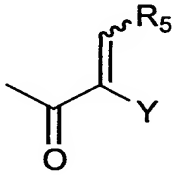
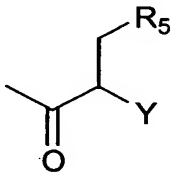
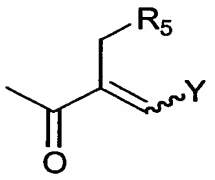
W, A and B taken together with the groups to which they are associated comprise




, or

W and A taken together with the groups to which they are associated comprise

and B is

wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

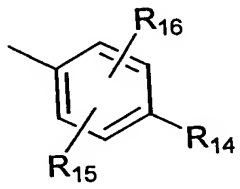
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

R_1 is hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

R_1 is hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, then

W is not hydrogen;

when

R_1 is hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

when

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_1 is not hydrogen, or $C(O)R_A$ where R_A is alkyl or an amino acid.

2. A method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; artherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "first therapeutic indications") which comprises

administering to a subject a therapeutically effective amount of one or more compounds of the formula I as defined in claim 1.

3. Use of compounds of the formula I for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications according to claim 2.

4. Use of one or more compounds of the formula I in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications according to claim 2.

5. An agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications according to claim 2 which comprises one or more compounds of the formula I either alone or in association with one or more carriers or excipients.

6. A therapeutic composition which comprises one or more compounds of the formula I in association with one or more pharmaceutical carriers and/or excipients.

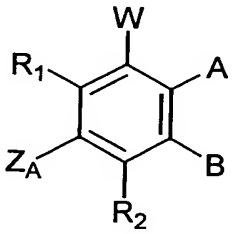
7. A drink or food-stuff, which contains one or more compounds of the formula I.

8. A microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds of the formula I.

9. One or more microorganisms which produce one or more compounds of the formula I.

10. A method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual

syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; atherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "second therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds of the formula II:



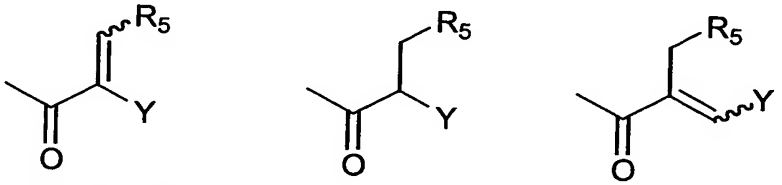
(II)

in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

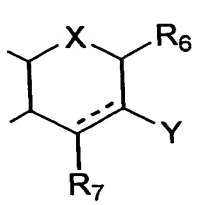
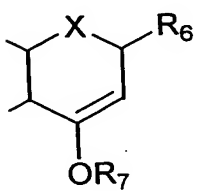
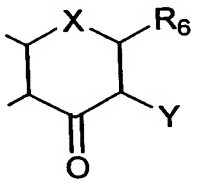
Z_A is hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from



, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from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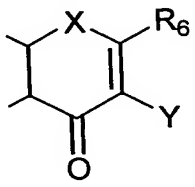
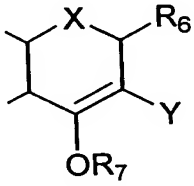
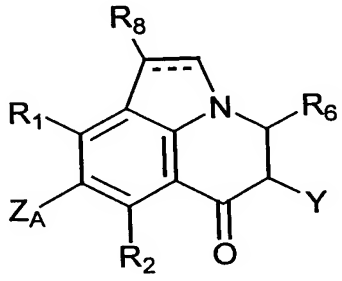
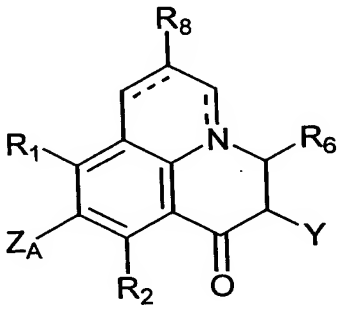
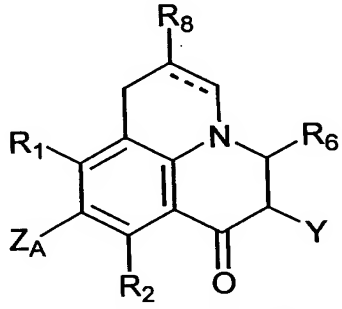
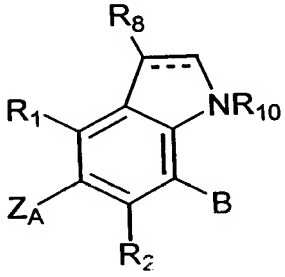
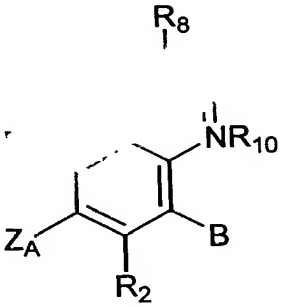
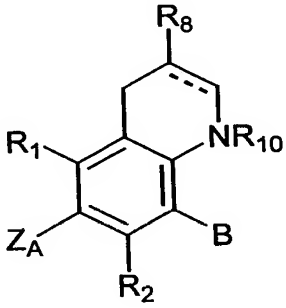



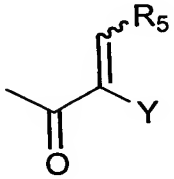
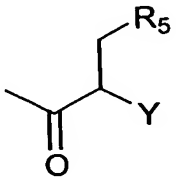
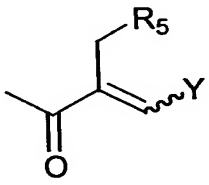
W, A and B taken together with the groups to which they are associated comprise




, or

W and A taken together with the groups to which they are associated comprise

and B is

wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen which they are attached are pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

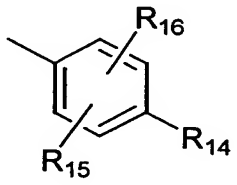
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo.

11. Use of compounds of the formula II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications according to claim 10.

12. Use of one or more compounds of the formula II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications according to claim 10.

13. An agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications according to claim 10 which comprises one or more compounds of the formula II either alone or in association with one or more carriers or excipients.

DATED this 6th day of September 1999.

NOVOGEN RESEARCH PTY LTD

By Its Patent Attorneys

DAVIES COLLISON CAVE